IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Gariepy	
Application No.: 09/601,644	
Filed: 12/11/2000	Group Art Unit: 1639
Title: Cytotoxic Heteromeric Protein Combinatorial Libraries	Examiner: M. L. Shibuya
	Confirmation No. 7797
Attorney Docket No.: MMC.P-001	

REPLY BRIEF FOR APPELLANT

This reply brief is filed in support of Applicants' Appeal from the final rejection mailed 7/12/2007, and in response to the Examiner's Answer mailed May 14, 2008.

The only rejections outstanding in this case relate to compliance with the written description and enablement requirements of 35 USC § 112, first paragraph. The Examiner in a highly repetitive and verbose presentation in which every argument every made (whither or not it remains relevant) focuses in one the failure to provide characterization of the specific products. Appellants respectfully point out, however, that the claims at issue in this case are method claims. As such, what is required is a description and enablement of the method, not of every possible product that could be made by the method.

In the Examiner's Answer, on 22, the Examiner begins an actual response to the Appeal Brief. The Examiner states that "he does not find, as a claimed limitation, the step of testing cells to find those insensitive to the wild type protein." Appellants respectfully point out that claim 1 requires that the "screening cells are insensitive to the selected cytotoxic heteromeric protein toxin at the concentration used in the screening." The Examiner has not explained why the enablement or written description of the invention is lacking simply because Appellants do not expressly recite a stop in which this knowledge is gained.

The Examiner next states (Page 24) that he "respectfully submits that the claimed invention encompasses genera of prophetic binding domain variants of unspecified RIP proteins, which are selected by prophetic functional cytotoxic assays, and that bind to totally unknown receptors." Appellants point out again that the claims do not expressly cover even one binding domain variant. The claims are **method claims** directed to a way of making binding domain variants. The claims make use of a genus of RIP proteins, and the assay is fully defined. It is exemplified with real examples and is not merely prophetic. Furthermore, the whole point of the assay is that the receptor targeted by the modified binding domain does not have to be known or characterized.

The Examiner also asserts that Appellants argument substitutes argument for evidence in an unpredictable art. The Examiner has not, however, offered any reasoning as to why the logic argued is in error. Absent some effort to show that the Examiner has logic on his side, Appilcants is not required to present evidence. The issue is whether the variant binding domain (VBD) binds to some other receptor than the one to which unmutated wild-type binding domain (WTD) binds. The logic is simple:

Binding is required for toxicity.

WTD is not toxic.

therefore, WTD does not bind

VBD is toxic,

therefore VBD does bind.

receptor that binds to VBD but not to WTD has a different specificity from receptor that binds to WTD.

Appellants are not sure what other evidence the Examiner seeks beyond the evidence that makes up the facts relied on in this logical progression. The assay process always relies on these facts being true. Thus, in other applications of the method, the variant binding domain will have different specificity from the wild type domain, or it will not be selected in the method.

The Examiner reiterates his position that there is no written description because there is allegedly not enough evidence of knowledge in the art of RIP sequences. The examiner fails to

respond to the fact that Appellants' invention takes advantage of the properties of RIPs to provide a method for making proteins that bind to different receptors, **but this use requires no knowledge of the starting sequence of the protein**. If no sequence knowledge is required to use the method, it cannot be required to comply with the written description or the enablement requirement.

With respect to enablement the examiner states that "Appellants argument in the brief that simply screening any cells against RIP toxins will produce cells insensitive to RIP toxins is not supported by any proferred evidence." (Page 27). This is likely to be because Appellants **did not make such an argument.** Nothing about screening produces cells that are insensitive. Rather, screening is used to identify RIP toxins to which the cells are inherently insensitive. This is why Appellants argued that:

> These cells already exist. All that is required is pairing a cell of interest with an appropriate RIP that does not bind to the surface of that cell as reflected by insensitivity to the toxin. In the unlikely event that some cell should possess every surface marker to which an RIP binds, then use of that cell would not fall within the scope of the claims since these cells could not be "insensitive to the selected cytotoxic heteromeric protein toxin at a concentration used in the screening" as required in the claims.

The Examiner also argues that there might be many reasons why a cell might be insensitive to a toxin. The reasons are taken from drug resistance art, and the Examiner has not explained how these would apply to make a cell insensitive to a toxin. For example, what target protein would be amplified in order to render a cell resistance to an RIP toxin. More receptor would make it more sensitive, not less.

The Examiner also argues that the insensitivity might be due to an increased toxin efflux. Then, on page 28, the Examiner criticizes the brief stating that "Appellants argument in the brief that if cells are insensitive to a toxin through some other mechanism than the failure to bind, it will not suddenly become sensitive through mutation of the toxin's dining domain ... has not been supported by furnishing objective evidence and appears to be mere attorney argument." Since the Examiner is indulging in speculation, logical argument to show this speculation is illogical and

unfounded is indeed a highly appropriate and the only required response. The new speculative example (binding to a different epitope of the receptor) misses the point because this is not the situation to which Appellants argument was directed.

Rather, it is in this fact pattern the examiner argues and which Appellants argument responds to:

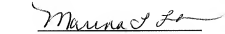
WTD binds so toxin gets into cell, but fails to be toxic because of rapid toxin efflux.

VBD also binds, so toxin gets into cell.

by the Examiner's logic, the mutation to the toxin BD makes the cell efflux mechanism different, even though neither the toxin domain nor the cell were changed. This is illogical and makes no sense. Even if the VBD binds to a different epitope of the receptor, there is no evidence, or scientific logic that the efflux of the toxin would be different.

In view of the foregoing, and the previously submitted Brief for Appellants, Appellants submit that all claims of this application are in form for allowance and that the rejections should be reversed. Such action is respectfully requested.

Respectfully submitted,



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